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Relation Of Penicillin To Metabolic Activity

L. O. Krampitz, Ph.D.*

IN RECENT years chemotherapy has become increasingly important in all branches of medicine. The advent of antibiotics has provided a means by which many of the infectious diseases can be treated with remarkable success. Continued progress with synthetic chemicals and antibiotics is to be expected in the next few years. Such progress is dependent upon a more fundamental knowledge of the mode of action of these chemotherapeutic agents. In the past most research has been devoted to the discovery of new agents without much thought as to their mode of action. The method of "screening" new compounds for their beneficial effects has yielded remarkable results. However, the time has come when as an important adjunct to this type of research the fundamental aspect of the mode of action must accompany the former method.

Briefly stated, the problem is to determine how the chemotherapeutic agents affect the various enzymic systems in the cell. As our knowledge of cellular metabolism increases we are able to study the mode of action of these drugs in more detail. Of late much emphasis has been placed on the structural relationship between the chemical constitution of accessory metabolites and the drug. The antagonistic relationship between para-amino benzoic acid and sulfanilamide is a familiar example. It is well known that para-amino benzoic acid will antagonize the effect of sulfanilamide on organisms susceptible to the drug. A clearer under-

standing of the mechanism involved would no doubt be obtained if the metabolic function of para-amino benzoic acid was known.

Recently work has been conducted in our laboratories on the mechanism of action of penicillin. It is generally known that this antibiotic inhibits the growth of certain microorganisms and that it is bacteriostatic in its behavior. From a metabolic point of view it can be expected that penicillin inhibits one or more vital enzymatic processes of susceptible organisms. Experimental procedures must be designed to determine what enzymatic processes are affected. The criterion of growth is not satisfactory since it measures the over-all processes which occur in the cell. The technique employing non-proliferating cells has been very useful. The bacteria are cultivated in mass quantities, centrifuged and the various metabolic substrates are added to suitable portions of the cell paste. Normally under these conditions no growth occurs, but enzymatic activity can be observed by measuring the oxygen uptake and/or the carbon dioxide evolution under a variety of conditions. The disappearance of the substrate and accumulation of end products in the presence and absence of the drug are also determined.

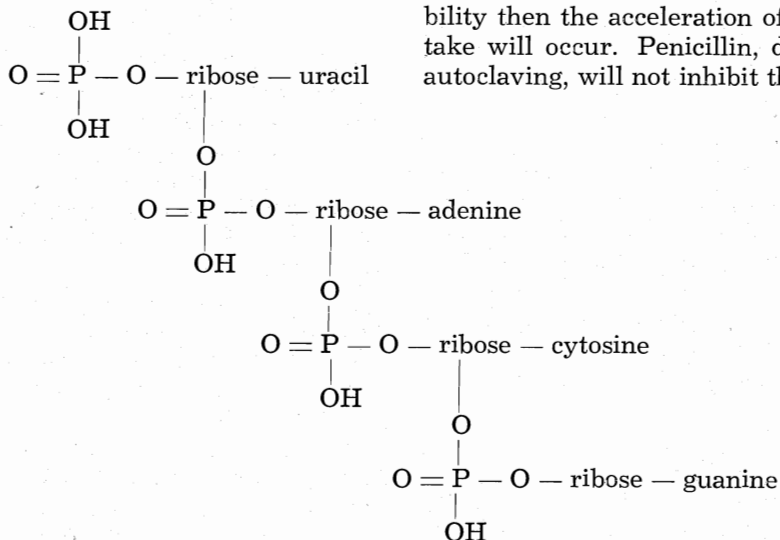
If a properly-buffered cell suspension is allowed to incubate there will be a lag phase during which there will be a small and constant rate of oxygen uptake for a period of 4 to 6 hours followed by a rapid acceleration. The oxygen uptake during the lag period represents the oxidation of reserve foodstuffs in the cell which

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is not inhibited by penicillin. The acceleration which occurs after the lag phase is completely inhibited by the drug. The problem was to elucidate what substances were being oxidized during the acceleration. Acetic acid and carbon dioxide are end products of this oxidation. The ratio of oxygen uptake to carbon dioxide evolved to acetic acid produced is 3:3:1. An equation which satisfies these conditions is:



which represents the oxidation of a pentose sugar. Of the pentoses which exist in the cell, ribose apparently is the most important since it is a constituent of that important class of compounds, the nucleic acids. The nuclei of animal and plant cells contain large amounts of ribonucleic acid. Bacteria have no differentiated nucleus but nevertheless possess nucleic acids which in all probability are important for reproduction. Structurally the nucleic acid can be represented as follows:



If one determines the amount of ribonucleic acid in *Staph. aureus* by measuring the total ribose prior to the acceleration of oxygen uptake, and again after the oxidation has taken place one will find that the ribonucleic acid content of the cell decreases remarkably. In the presence of penicillin this decrease does not occur. Apparently the nucleic acids

are being enzymatically decomposed and the ribose is subsequently oxidized. Since penicillin will not inhibit the oxidation of ribose when added to the cells, the inhibition observed during the endogenous activity must involve the dissimilation of the nucleic acids into their component parts. Assuming that reactions of this type are reversible we may say that the synthesis of nucleic acid as well as their decomposition is inhibited by penicillin.

One might at first conclude that the drug is exerting a general toxic effect on the cell and consequently the cell cannot oxidize the ribose constituent of the nucleic acid. Experimental evidence definitely shows this is not the case. If glucose is added to a cell suspension in which the cells and the penicillin have been in contact during the lag period, the glucose will be immediately oxidized. If general toxicity were the cause of inhibition the glucose could not be oxidized. Furthermore, if a cell suspension which contains penicillin is incubated until the penicillin content decreases because of its instability then the acceleration of oxygen uptake will occur. Penicillin, destroyed by autoclaving, will not inhibit the oxidation.

Ribonucleic acid, isolated from yeast, when added to the cells as a substrate shortens the lag period and the maximum rate of oxidation attained after the acceleration period is greater than the endogenous activity. Penicillin completely inhibits this activity. The similarity in behavior of the endogenous activity with that of added yeast nucleic acid strength-

ens the evidence that penicillin affects nucleic acid metabolism of the cell.

The few preliminary experiments cited here are significant enough to indicate which class of compounds is involved in the inhibition by penicillin during the cellular metabolism of an organism susceptible to the drug. The biosynthesis of nucleic acids is very complex and to predict which specific step penicillin is inhibiting is difficult.

It is significant that streptomycin will inhibit this nucleic acid dissimilation in much the same manner as penicillin. However, the 2 antibiotics may be bringing about their deleterious effect by inhibiting entirely different reactions in the chain of nucleic acid synthesis. The determination of oxygen uptake or nucleic acid disappeared in our experiments is the measurement of an over-all process. Inhibiting of any one of the steps involved would result in inhibition of the entire dissimilation of the nucleic acid. Consequently many of the antibiotics may have the same effect as inhibition as measured in our experiments and yet each may have specificity depending upon what reactions are required by individual organisms for the synthesis of nucleic acids.

The freon gas bomb now being used with success against mosquitoes by the armed forces is, with slight modifications, equally effective against bacteria, according to officials of the United States Department of Agriculture. With it the air of offices, schoolrooms and other places of assembly may be freed of many varieties of germs.

NOTICE

The following issues of *The Veterinary Student* are depleted from our reserve file:

Vol. I, No. 1, 1939, and No. 3, 1940.

Vol. II, No. 2, 1941, and No. 3, 1941.

Vol. III, No. 1, 1941, and No. 2, 1942.

Vol. IV, No. 2, 1943.

Vol. V, No. 4, 1944.

We would greatly appreciate receiving any of these issues from our readers. They are to be used to complete the files of several educational libraries.

Studies conducted by the Bureau of Animal Industry to determine the longevity of *Bacillus anthracis* in the carcasses of animals which have died of anthrax have yielded the following results: Few, if any, organisms survive in the unopened carcass after 72 to 80 hours if the temperature is held at 28° to 30° C. or higher. This is due to the fact that the anthrax bacilli are destroyed by the anaerobic organisms producing putrefaction in the unopened carcass. The opposite of this was true in unopened carcasses held at ice-box temperatures. These results seem to indicate that in the unopened carcasses of animals dead of anthrax during the hot months of summer the anthrax organisms are destroyed in from 3 to 4 days. However, during the colder months of the year the organisms may live in the tissues and blood of an unopened carcass for at least 4 weeks. Opening the carcass in either case will result in vegetative sporulation with spores that will persist for a much longer period of time.

It has been stated that severe hepatic injury is invariably associated with a deficiency of prothrombin in the circulating blood. If the hepatic injury is severe enough, the administration of vitamin K is not effective in correcting the deficiency of prothrombin. It is believed that disease of the liver interferes with response of the prothrombin level to vitamin K therapy. Transfusion of blood fortified by the administration of vitamin K to the donors was used as a temporary aid in controlling hemorrhage in 4 cases of severe acute damage to the liver. The results obtained from this method of treatment indicate that the method may have definite value in preventing death from immediate hemorrhage or in control of hemorrhage until the regeneration of sufficient hepatic tissue for essential functions.

Woodchucks, muskrats, opossums, rats, beavers, pheasants and other game birds as well as rabbits, may be vectors of tularemia.